Exhibit A

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GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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ject insulin into their thigh may experience a precipitous drop in blood sugar that is not seen following injection into the arm or abdominal wall, since running markedly increases blood flow to the leg. Generally, the rate of absorption following injection of an aqueous preparation into the deltoid or vastus lateralis is faster than when the injection is made into the gluteus maximus. The rate is particularly slower for females after injection into the gluteus maximus. This has been attributed to the different distribution of subcutaneous fat in males and females, since fat is relatively poorly perfused. Very obese or emaciated patients may exhibit unusual patterns of absorption following intramuscular or subcutaneous injection. Very slow, constant absorption from the intramuscular site results if the drug is injected in solution in oil or suspended in various other repository vehicles. Penicillin often is administered in this manner. Substances too irritating to be injected subcutaneously may sometimes be given intramuscularly.

Intraarterial. Occasionally a drug is injected directly into an artery to localize its effect in a particular tissue or organ. However, this practice usually has dubious therapeutic value. Diagnostic agents are sometimes administered by this route. Intraarterial injection requires great care and should be reserved for experts. The first-pass and cleansing effects of the lung are not available when drugs are given by this route.

Intrathecal. The blood–brain barrier and the blood–cerebrospinal fluid barrier often preclude or slow the entrance of drugs into the CNS. Therefore, when local and rapid effects of drugs on the meninges or cerebrospinal axis are desired, as in spinal anesthesia or acute CNS infections, drugs are sometimes injected directly into the spinal subarachnoid space.

Intraperitoneal. The peritoneal cavity offers a large absorbing surface from which drugs enter the circulation rapidly, but primarily by way of the portal vein; first-pass hepatic losses are thus possible. Intraperitoneal injection is a common laboratory procedure, but it is seldom employed clinically. The dangers of producing infection and adhesions are too great to warrant the routine use of this route in human beings.

Pulmonary Absorption. Gaseous and volatile drugs may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the circulation is rapid by this route, because the surface area is large. The principles governing absorption and excretion of anesthetic and other therapeutic gases are discussed in Chapters 13, 14, and 16.

In addition, solutions of drugs can be atomized and the fine droplets in air (aerosol) inhaled. Advantages are the almost instantaneous absorption of a drug into the blood, avoidance of hepatic first-pass loss, and, in the case of pulmonary disease, local application of the drug at the desired site of action. For example, drugs can be given in this manner for the treatment of bronchial asthma (*see* Chapter 28). The main disadvantages are poor ability to regulate the dose, cumbersomeness of the methods of administration, and the fact that many gaseous and volatile drugs produce irritation of the pulmonary epithelium.

Pulmonary absorption is an important route of entry of certain drugs of abuse and of toxic environmental substances of varied composition and physical states (*see* Section XVII). Both local and systemic reactions to allergens may occur subsequent to inhalation.

Topical Application. *Mucous Membranes.* Drugs are applied to the mucous membranes of the conjunctiva, nasopharynx, oropharynx, vagina, colon, urethra, and urinary bladder primarily for their local effects. Occasionally, as in the application of antidiuretic hormone to the nasal mucosa, systemic absorption is the goal. Absorption through mucous membranes occurs readily. In fact, local anesthetics applied for local effect sometimes may be absorbed so rapidly that they produce systemic toxicity.

Skin. Few drugs readily penetrate the intact skin. Absorption of those that do is proportional to the surface area over which they are applied and to their lipid solubility, since the epidermis behaves as a lipid barrier (*see* Chapter 64). The dermis, however, is freely permeable to many solutes; consequently, systemic absorption of drugs occurs much more readily through abraded, burned, or denuded skin. Inflammation and other conditions that increase cutaneous blood flow also enhance absorption. Toxic effects sometimes are produced by absorption through the skin of highly lipid-soluble substances (*e.g.*, a lipid-soluble insecticide in an organic solvent). Absorption through the skin can be enhanced by suspending the drug in an oily vehicle and rubbing the resulting preparation into the skin. This method of administration is known as *inunction*. Because hydrated skin is more permeable than dry skin, the dosage form may be modified or an occlusive dressing may be used to facilitate absorption. Controlled-release topical patches are recent innovations. A patch containing scopolamine, placed behind the ear where body temperature and blood flow enhance absorption, releases sufficient drug to the systemic circulation to protect the wearer from motion sickness. Transdermal estrogen replacement therapy yields low maintenance levels of estradiol while minimizing the high estrone metabolite levels observed following oral administration.

Eye. Topically applied ophthalmic drugs are used primarily for their local effects (*see* Chapter 65). Systemic absorption that results from drainage through the nasolacrimal canal is usually undesirable. In addition, drug that is absorbed after such drainage is not subject to first-pass hepatic elimination. Unwanted systemic pharmacological effects may occur for this reason when β-adrenergic antagonists are administered as ophthalmic drops. Local effects usually require absorption of the drug through the cornea; corneal infection or trauma may thus result in more rapid absorption. Ophthalmic delivery systems that provide prolonged duration of action (*e.g.*, suspensions and ointments) are useful additions to ophthalmic therapy. Ocular inserts, developed more recently, provide continuous delivery of low amounts of drug. Very little is lost through drainage; hence, systemic side effects are minimized.

Bioequivalence. Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be bioequivalent when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions. In the past, dosage forms of a drug from different manufacturers and even different lots of preparations from a single manufacturer sometimes differed in their bioavailability. Such differences were seen primarily among oral dosage forms of poorly soluble, slowly absorbed drugs. They result from differences in crystal form, particle size, or other physical characteristics of the drug that are not rigidly controlled in formulation

and manufacture of the preparations. These factors affect disintegration of the dosage form and dissolution of the drug and hence the rate and extent of drug absorption.

The potential nonequivalence of different drug preparations has been a matter of concern. Strengthened regulatory requirements have resulted in few, if any, documented cases of nonequivalence between approved drug products. The significance of possible nonequivalence of drug preparations is further discussed in connection with drug nomenclature and the choice of drug name in writing prescription orders (*see* Appendix I).

DISTRIBUTION OF DRUGS

After a drug is absorbed or injected into the bloodstream, it may be distributed into interstitial and cellular fluids. Patterns of drug distribution reflect certain physiological factors and physicochemical properties of drugs. An initial phase of distribution may be distinguished that reflects cardiac output and regional blood flow. Heart, liver, kidney, brain, and other well-perfused organs receive most of the drug during the first few minutes after absorption. Delivery of drug to muscle, most viscera, skin, and fat is slower, and these tissues may require several minutes to several hours before steady state is attained. A second phase of drug distribution may therefore be distinguished; this is also limited by blood flow, and it involves a far larger fraction of the body mass than does the first phase. Superimposed on patterns of distribution of blood flow are factors that determine the rate at which drugs diffuse into tissues. Diffusion into the interstitial compartment occurs rapidly because of the highly permeable nature of capillary endothelial membranes (except in the brain). Lipid-insoluble drugs that permeate membranes poorly are restricted in their distribution and hence in their potential sites of action. Distribution also may be limited by drug binding to plasma proteins, particularly albumin for acidic drugs and α_1-acid glycoprotein for basic drugs. An agent that is extensively and strongly bound has limited access to cellular sites of action, and it may be metabolized and eliminated slowly. Drugs may accumulate in tissues in higher concentrations than would be expected from diffusion equilibria as a result of pH gradients, binding to intracellular constituents, or partitioning into lipid.

Drug that has accumulated in a given tissue may serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation. An example that illustrates many of these factors is the use of the intravenous anesthetic thiopental, a highly lipid-soluble drug. Because blood flow to the brain is so high, the drug reaches its maximal concentration in brain within a minute after it is injected intravenously. After injection is concluded, the plasma concentration falls as thiopental diffuses into other tissues, such as muscle. The concentration of the drug in brain follows that of the plasma, because there is little binding of the drug to brain constituents. Thus, onset of anesthesia is rapid, but so is its termination. Both are directly related to the concentration of drug in the brain. A third phase of distribution for this drug is due to the slow, blood-flow–limited uptake by fat. With administration of successive doses of thiopental, accumulation of drug takes place in fat and other tissues that can store large amounts of the compound. These can become reservoirs for the maintenance of the plasma concentration, and therefore the brain concentration, at or above the threshold required for anesthesia. Thus, a drug that is short acting because of rapid redistribution to sites at which the agent has no pharmacological action can become long acting when these storage sites are "filled" and termination of the drug's action becomes dependent on biotransformation and excretion (*see* Benet, 1978).

Since the difference in pH between intracellular and extracellular fluids is small (7.0 vs. 7.4), this factor can result in only a relatively small concentration gradient of drug across the plasma membrane. Weak bases are slightly concentrated inside of cells, while the concentration of weak acids is slightly lower in the cells than in extracellular fluids. Lowering the pH of extracellular fluid increases the intracellular concentration of weak acids and decreases that of weak bases, provided that the intracellular pH does not also change and that the pH change does not simultaneously affect the binding, biotransformation, or excretion of the drug. Elevating the pH produces the opposite effects (*see* Figure 1–2).

Central Nervous System and Cerebrospinal Fluid. The distribution of drugs to the CNS from the bloodstream is unique, mainly in that entry of drugs into the cerebrospinal fluid and extracellular space of the CNS is restricted. The restriction is similar to that across the gastrointestinal epithelium. Endothelial cells of the brain capillaries differ from their counterparts in most tissues by the absence of intercellular pores and pinocytotic vesicles. Tight junctions predominate, and aqueous bulk flow thus is severely restricted. This is not unique to the CNS capillaries (tight junctions appear in many muscle capillaries as well). It is likely that the unique arrangement of pericapillary glial cells also contributes to the slow diffusion of organic acids and bases into the CNS. The drug molecules probably must traverse not only endothelial but also perivascular cell membranes before reaching neurons or other target cells in the CNS. Cerebral blood flow is the only limitation to permeation of the CNS by highly lipid-soluble drugs. The rate of diffusion of drugs with increas-

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consistent, and the presence of food may enhance or diminish the absorption of drugs. The most common type of interaction occurs when a food constituent binds the drug and the food-drug complex cannot pass through the gut wall. For example, complexation of tetracycline antibiotics may occur when these drugs are administered with dairy products or with antacids containing aluminum, calcium, or magnesium. The presence of a large meal in the stomach will delay gastric emptying. If a drug that is absorbed in the intestine is ingested with a large meal, the delay in gastric emptying may result in a delay in absorption of the drug. However, the presence of food in the stomach has also been shown to *increase* absorption of some drugs. For example, the bioavailabilities of the β-adrenergic blocking drugs, propranolol and metoprolol, are enhanced by the presence of food.[3] Therefore, because of the difficulty in predicting the absorption pattern of a drug in the presence of food, it is usually advisable to administer drugs when the stomach is empty. An exception to this advice is with drugs which cause gastrointestinal irritation and nausea. These drugs must be given with food to prevent these side effects. It is recommended that such drugs *always* be taken with food to compensate for the differences in absorption that might occur if they were given one time with food and another time without food.

Water taken concomitantly with certain drugs may increase bioavailability. The administration of aspirin, erythromycin stearate, amoxicillin or theophylline with 250 mL of water results in greater bioavailability than if the same drugs are ingested with only 25 mL of water.[4] It is probable that the increased amount of water enhances the amount of drug absorbed by improving drug dissolution as well as by hastening gastric emptying.

Diseases that affect the structure and function of the gastrointestinal tract are also capable of altering the absorption of drugs after oral administration. However, no consistent pattern develops; rather, there appears to be a complex relationship between the effect of the disease on stomach and intestinal functions and the absorption of the drug in question. For example, diseases such as diabetes mellitus or chronic renal failure, diseases that delay gastric emptying, will markedly delay the absorption and onset of effect of drugs that must reach the small intestine before they are absorbed. This has been a problem with the use of phenytoin in patients with chronic renal failure. Celiac disease and Crohn's disease, two diseases that alter the intestinal epithelium, have been studied in detail.[5] In these diseases, absorption of some drugs is greatly affected, but there is no consistent pattern of altered drug absorption.

When a drug is to be administered orally to a patient with altered gastrointestinal motility, diseases of the stomach and small or large intestine, previous stomach or intestinal surgery, or gastrointestinal infection, there is a considerable probability that drug absorption characteristics in these patients will differ from those in healthy volunteers. This may result in a change in the time of peak blood level or the extent of absorption. It is advisable to observe such patients closely for clinical effect during initial drug administration and during chronic dosing in order to assess the influence of alterations in absorption and to correct dosing regimens accordingly. The monitoring of drug blood concentrations may be beneficial in adjusting dose.

Non-Oral Routes—Drugs are administered by a variety of non-oral routes. These include: subcutaneous, intramuscular, intravenous, inhalation, percutaneous, buccal, sublingual, rectal, vaginal, intra-arterial and intrathecal. In the cases of inhalation, topical application to the skin or mucous membranes, rectal, vaginal, intra-arterial or intrathecal administration, the route is often chosen to ensure that drugs reach a specific site with a minimum of systemic absorption. The rationale is that the maximum concentration of drug will be at the site of action so that side effects will be lessened. Nevertheless, if large doses are administered by these routes, enough drug may reach the general circulation to produce side effects. Therefore, the dose and preparation should be such that limited quantities of drug reach the systemic circulation. The beta-adrenergic agonists, metaproterenol and albuterol, when administered by inhalation produce bronchodilatation at doses that avoid serious systemic side effects. Similarly, the corticosteroid, beclomethasone, can also be administered by this route for the management of chronic asthma. Low doses of beclomethasone by inhalation are without the serious systemic side effects of oral steroids. However, as the dose is increased beyond two inhalations four times a day, for an average daily dose of 400 μg, there is a greater incidence of side effects, including adrenal suppression.

The *topical* administration of drugs is rapidly becoming an important route of drug administration of systemic drugs. Previously used only for the application of drugs for local effects in diseases of the skin, it is now being explored as a means of administering drugs for their systemic effects. Nitroglycerin is commonly applied to the skin in the form of an ointment or transdermal patches; it is rapidly absorbed and provides sustained blood levels. Sublingual nitroglycerin is also employed to produce therapeutic blood levels; it produces a maximal effect on anginal pain within 3 to 5 mins but lasts only 20 to 60 min. In contrast, nitroglycerin ointment provides peak blood concentrations in about one hour and the effect on anginal pain may last for several hours. The sublingual tablets should be used to suppress acute angina attacks, whereas nitroglycerin ointment or transdermal patches may be useful to prevent recurrence of episodes of angina for prolonged periods, such as during the night. Whether or not the continuous administration of nitrates by this route will result in the development of tolerance is not clear at this time. There are several other drugs, such as those used to treat hypertension, for which percutaneous administration is being investigated as a means of attaining sustained plasma levels.

Close *intra-arterial* administration of drugs is used to get drugs directly to a target site or organ in high concentration. After it has passed through the target region it is distributed in the entire blood volume, which reduces the systemic levels of the drug and the consequent side effects. One example of this mode of drug administration is the use of cytotoxic drugs for the treatment of primary or metastatic tumors of liver. The infusion of drugs into the hepatic artery exposes the tumor to higher drug concentrations than can be tolerated with intravenous administration. If the drug is efficiently extracted by liver, the exposure of sensitive tissues such as bone marrow and gastrointestinal epithelium to the drug will be decreased. For example, after hepatic artery infusion of floxuridine (FUDR) hepatic vein concentrations are 2 to 6 times higher than comparable drug concentrations following intravenous infusion yet systemic blood concentrations are 75% less. Thus, the therapeutic index of FUDR in the treatment of liver cancer is considerably increased by hepatic arterial infusion. This type of selective drug administration may be beneficial with other drugs that have low therapeutic indices.

Intrathecal injection is used to deliver drugs to the brain in sufficient concentration to produce an effect but at the same time to reduce the incidence or severity of systemic side effects. The intrathecal administration of the cancer chemotherapeutic agent, methotrexate, is frequently employed in the management of leukemic involvement of the central nervous system. The epidural administration of morphine, which produces long-lasting (6–30 hrs) analgesia with minimal side effects, is proving to be of benefit in the management of chronic pain.

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Comparison between Intraperitoneal and Oral Methylphenidate Administration: A Microdialysis and Locomotor Activity Study[1]

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Abstract

The therapeutic and stimulant properties of methylphenidate (MP), a drug commonly prescribed for the treatment of attention deficit hyperactivity disorder, have been attributed to increases in synaptic dopamine (DA) concentrations resulting from the blockade of DA transporters. In addition to obvious difficulties inherent in any interspecies comparison, interpretation of preclinical studies done with MP is further complicated by different routes of administration in animals (i.v. and i.p.) compared with humans (oral). In the present study we compared the effects of i.p. and intragastric (oral) MP both on rat nucleus accumbens DA assessed by in vivo microdialysis and on locomotor activity measured in a photocell apparatus. We also compared regional brain uptake and plasma levels of [^{3}H]MP after administration of 5 mg/kg via both routes. Intraperitoneal MP (5 and 10 mg/kg) was approximately twice as potent as intragastric MP in terms of increasing extracellular DA levels and in stimulating locomotion. This

was consistent with the higher brain uptake of [^{3}H]MP when given i.p. rather than intragastrically. The dose of 2 mg/kg produced significant increases in both measurements when administered i.p., but not intragastrically. This study shows that relatively low doses of MP (2 mg i.p. and 5 mg intragastric) significantly increase extracellular DA and locomotor activity and indicates that the differences in the neurochemical and behavioral effects of MP between the intragastric and the i.p. routes are due to central drug bioavailability.

Introduction

Over the past decade increased recognition of attention deficit hyperactivity disorder (Swanson et al., 1998) has led to a dramatic increase in the use of methylphenidate (Ritalin, MP), a psychostimulant commonly prescribed to treat this disorder. Despite this widespread use, the mechanisms by which MP exerts its therapeutic effects remain poorly understood. Although a considerable number of preclinical studies have been completed, their interpretation is limited by the fact that i.p. and i.v. routes have been used, whereas the oral route is used clinically. Moreover, most studies have used doses significantly higher (2-15 mg/kg i.v. or 10-50 mg/kg i.p.) than those used clinically in humans (0.3-1 mg/kg; Sprague and Sleator, 1977). Studies with doses that are therapeutically relevant (0.6-10 mg/kg i.p. or s.c.) have predominantly investigated sensitization and tolerance to motor-activating and stereotypic effects of MP (McNamara et al., 1993; Gaytan et al., 1997; McDougall et al., 1999). Higher doses of MP lead to a greater incidence of side effects, including sleep disturbances and irritability in children (Cole, 1975). To our knowledge, the only two studies that have investigated the effects of oral MP in rodents focused on its pharmacokinetic profile in brain and plasma, and not on the concomitant behavioral or neurochemical effects of the drug (Wargin et al., 1983; Patrick et al., 1987).

The therapeutic effects of MP as well as its psychostimulant properties are thought to be related to its ability to increase extracellular dopamine (DA) in the mesocorticolimbic system (Castellanos et al., 1996), secondary to blockade of DA transporters (Ritz et al., 1987). Similarly, the reinforcing effects of cocaine and cocaine-like drugs also are associated with their ability to block the DA transporter. This has led to serious concerns regarding the potential reinforcing or addictive properties of MP. However, despite the pharmacological similarities between MP and cocaine, including similar potency at the DA transporter (Volkow et al., 1995; Gatley et al., 1999), its abuse is much less frequent (NIDA-CEWG, 1995) and is mainly restricted to the i.v. or intranasal route of administration with very infrequent oral abuse (Parran and Jasinski, 1991). The rare occurrence of oral abuse is probably related to the slow rate of DA transporter blockade achieved by oral MP because the reinforcing effects of psychostimulant drugs are thought to be related, at least in part, to a

rapid rate of binding to DA transporters (Stathis et al., 1995) and subsequently, a rapid increase in synaptic DA (Balster and Schuster, 1973). Thus, although i.v. MP produces a "high", which cocaine abusers report to be similar to that induced by i.v. cocaine (Wang et al., 1997), oral MP with a slower onset of transporter blockade does not produce a high in normal subjects (Volkow et al., 1998).

Dose-related effects of MP were clearly demonstrated by Porrino and coworkers. They showed that local cerebral glucose utilization (LCGU) in the rat nucleus accumbens (NACC), a brain region associated with the reinforcing effects of drugs of abuse (Di Chiara, 1999), was stimulated by a low dose of MP (1.25 mg/kg i.v.), but not by a high dose (15 mg/kg). However, higher doses dramatically increased LCGU in the extrapyramidal system (Porrino and Lucignani, 1987). A similar dose-related pattern was observed with amphetamine (Porrino et al., 1984). These authors later demonstrated that behaviorally equivalent doses of i.v., but not i.p. cocaine, produced increases in LCGU in NACC (Porrino, 1993). This similarity in the distribution of changes in LCGU led the authors to propose a significant role of the NACC in the therapeutic response of hyperactive children to psychostimulant medications. Taken together, these data suggest the importance of determining the dose-response function for different routes of administration in evaluating the biochemical and behavioral effects of psychostimulants.

The purpose of the present study was to assess the effects of oral MP (intragastric administration) on extracellular DA in NACC and on locomotor activity. In addition, we directly compared the effects of oral versus i.p. MP to provide a context for evaluation of the findings from previous studies. The range of doses used (2-10 mg/kg) is, in general, lower than those investigated previously. Finally, we compared two methods of oral MP administration, a surgically implanted intragastric catheter versus gavage, to determine whether the stress associated with gavage would influence the effects of MP on NACC DA.

Materials and Methods

Male Sprague-Dawley rats were used in all experiments (200-300 g; Taconic Farms, Germantown, NY) and were given food and water ad libitum. Temperature and humidity were kept constant. Each animal was housed individually on a 12/12-h light/dark cycle. All animals were used under an Institutional Animal Care and Use Committee-approved protocol and with strict adherence to National Institutes of Health guidelines.

Drug Treatment. MP hydrochloride (2, 5, or 10 mg/kg) (a racemic mixture of *d-threo-* and *l-threo-*MP; Research Biochemicals International, Natick, MA) was dissolved in saline and injected i.p.

Intragastric administration (2, 5, or 10 mg/kg) was accomplished through the preimplanted catheter followed by a rinse with vehicle. Control animals received saline via both routes. These same methods were used with microdialysis and locomotor activity studies. In a separate microdialysis experiment MP (5 mg/kg) or vehicle was administered via a gavage needle that was gently passed down the esophagus to the stomach (n = 6-8 for each treatment group). All microdialysis and activity measures were obtained between 12:00 PM and 3:00 PM.

Microdialysis Studies. Microdialysis studies were completed as detailed previously (Gerasimov and Dewey, 1999). Animals were anesthetized with an i.m. injection of ketamine/xylazine mixture and siliconized guide cannulas were stereotaxically implanted into the right NACC (2.0 mm anterior and 1.0 mm lateral to bregma, and 7.0 mm ventral to the cortical surface). On completion of the brain surgery a polyethylene catheter was placed in the stomach of animals intended for intragastric studies by using aseptic surgical techniques. The catheter was exteriorized after anchoring with a suture in the back of the neck. Animals were allowed to recover for at least 4 days.

Microdialysis probes (2.0 mm; Bioanalytical Systems, West Lafayette, IN) were positioned within the guide cannulas and artificial cerebrospinal fluid (155 mM NaCl, 1.1 mM $CaCl_2$, 2.9 mM KCl, and 0.83 mM $MgCl_2$) was administered through the probe by using a CMA/100 microinfusion pump (Bioanalytical Systems) at a flow rate of 2.0 l/min. Animals were placed in bowls, and probes were inserted and flushed with artificial cerebrospinal fluid overnight. On the day of study, a minimum of three samples was injected to determine baseline stability. Samples were collected for 20 min and injected on-line (Bioanalytical Systems). The average DA concentration of these three stable samples was defined as control (100%), and all subsequent treatment values were transformed to a percentage of that control. The HPLC system consisted of a BAS reversed phase column (3.0 μm C18), a BAS LC-4C electrochemical transducer with a dual glassy carbon electrode set at 650 mV relative to an Ag/AgCl reference electrode, a computer that analyzes data on-line by using a commercial software package (Chromgraph; Bioanalytical Systems), and a dual pen chart recorder. The mobile phase (flow rate 1.0 ml/min) consisted of 7.0% methanol, 50 mM sodium phosphate monobasic, 1.0 mM sodium octyl sulfate, and 0.1 mM EDTA, pH 4.0.

Locomotor Activity. Animals were individually placed in photocell activity boxes (San Diego Instruments, San Diego, CA). The boxes were 41.3 × 41.3 × 30.5-cm clear acrylic. The electronic system used to monitor the movements consists of 16 infrared beams projecting across the cages from left to right and 16 beams from back to back. All the beams are approximately 0.39 cm from the floor. After 100 min to allow initial exploratory behavior to decrease, animals were injected i.p. with vehicle or MP (2, 5, or 10 mg/kg). In a separate group of experiments, animals received saline or MP (2, 5, or 10 mg/kg) by intragastric infusion via a catheter. Beam crossings were recorded every

minute and the mean number of crossings for each group of animals was summed into 20-min intervals for graphical display.

***d*-[^{3}H]*threo*-MP Uptake in the Brain.** Animals were treated with 5 mg/kg MP plus 2 μCi (per rat) of *d*-[^{3}H]*threo*-MP either i.p. or via gavage. After 20 min animals were sacrificed by decapitation and their striata and cerebella dissected. Brain regions were weighed and dissolved in 1 ml of tissue solubilizer (Solvable; Packard, Meriden, CT). UltimaGold (Packard) liquid scintillation fluid was added and radioactivity was determined by scintillation counting with quench connection by external standard. Data are expressed as nanomoles of *d*-[^{3}H]*threo*-MP per gram of tissue (wet weight).

Data Analysis. Peak increases in extracellular DA, expressed as a percentage of baseline values (the average of three predrug levels differing from each other by not more than 10%) were compared for every dose across both routes of administration by a one-way ANOVA and post hoc test. Significance levels were set at $P < .05$.

For comparison purposes, the increases in NACC DA levels were normalized to the highest value for each dose and expressed as a percentage of that value. Locomotor activity reflects the highest beam crossing count after subtraction of the baseline activity.

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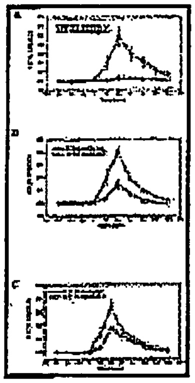
Microdialysis Studies. Intraperitoneal injections of MP dose dependently increased extracellular NACC DA above vehicle treatment values ($F = 26.75$; $P < .05$, $P < .01$, $P < .001$ for 2, 5, and 10 mg/kg, respectively). Intragastric administration also produced an increase in DA levels ($P < .05$ and $P < .001$ for 5 and 10 mg/kg, respectively). However, the measured response after intragastric administration of 2 mg/kg did not reach statistical significance. For both routes of administration and all three doses, the maximal effect of MP occurred at 40 min with levels returning to baseline values approximately 2.5 h postadministration (Fig. 1). During the first 20 min after administration the values approximately doubled for i.p. injection, but increased only by 30% after intragastric administration (Fig. 1, B and C), consistent with a faster rate of DA increase after the i.p. route.

Fig. 1. Temporal profile of i.p. or intragastrical (p.o.) MP effect on extracellular NACC DA. A, effects of 2 mg/kg MP. B, effects of 5 mg/kg MP. C, effects of 10 mg/kg MP. Values are expressed as percentage of baseline DA and are mean ± S.E. (n = 6-8/group). Drug or vehicle was administered at time 0. For clarity saline response is not shown.



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Administration of 5 mg/kg MP by gavage produced increases in DA levels that did not significantly differ from those produced by intragastric administration. The temporal profile of increases in extracellular DA after gavage administration is identical with the time course of increases after administration of the same dose via intragastric catheter (Fig. 2).

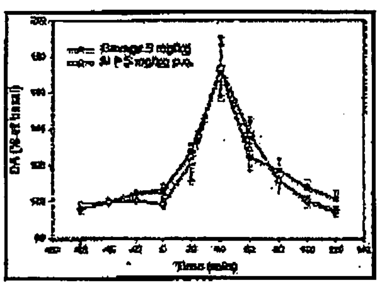

Fig. 2. Temporal profile of 5 mg/kg intragastrical (p.o.) and gavage MP effect on extracellular NACC DA. Values are expressed as percentage of baseline DA and are mean ± S.E. (n = 6-8/group). Drug was administered at time 0.

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Locomotor Activity. Similar to our microdialysis data, i.p. injections of MP dose dependently increased gross locomotor activity above vehicle treatment values (Fig. 3) (F = 36.68; $P < .05$, $P < .01$, $P < .001$ for 2, 5, and 10 mg/kg, respectively. Intragastric administration, however, resulted in increased locomotion only after 5- and 10-mg/kg doses ($P < .01$, $P < .001$). On average, the maximal response for i.p. administration occurred at 20 min, whereas for intragastric administration it occurred at 40 min postdrug administration. For each dose examined, the DAergic and locomotor response to i.p. MP was significantly greater than the response after intragastric administration (Figs. 4 and 5).

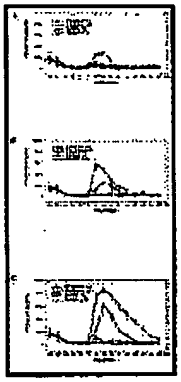

Fig. 3. Temporal profile of i.p. or intragastrical (p.o.) MP effect on gross locomotor activity. A, effects of 2 mg/kg MP. B, effects of 5 mg/kg MP. C, effects of 10 mg/kg MP. Values are expressed as the number of beam crossings and are mean ± S.E. (n = 6-8/group). Drug or vehicle was administered at time 0. For clarity saline response is not shown.

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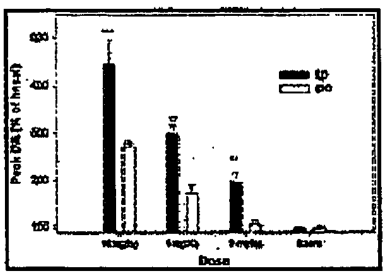

Fig. 4. Peak increase in NACC DA in response to i.p. or intragastrical (p.o.) administration of MP. Values are expressed as percentage of baseline DA and are mean ± S.E. (n = 6-8/group). ***P < .001, **P < .01 compared with the effect of the identical dose administered via different route [ANOVA (F = 26.75) and post hoc Tamhane test].

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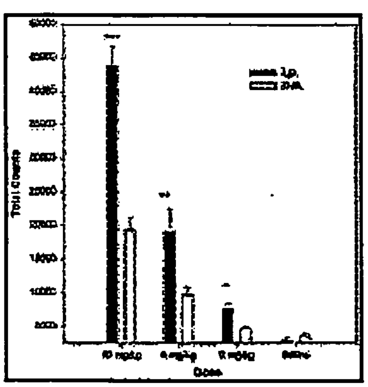

Fig. 5. Locomotor response to i.p. or intragastrical (p.o.) administration of MP. Values are expressed as total number of beam crossings over 200-min time interval and are mean ± S.E. (n = 6-8/group). ***P < .001, **P < .01, *P < .05 compared with the identical dose administered via different route [ANOVA (F = 36.68) and post hoc Tamhane test].

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The relationship between the temporal course of the changes in extracellular DA and locomotor activity is represented as a normalized response (Fig. 6). Because there was no change in either extracellular DA or locomotion after intragastric administration of 2 mg/kg, Fig. 5A shows only the response to i.p. injection.

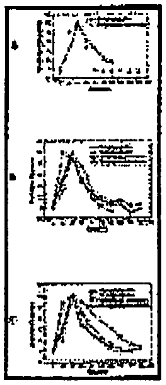

Fig. 6. Normalized NACC DA and locomotor temporal response to MP. Values are expressed as the percentage of the maximum for each given function and represent the average of six animals. Drug was administered at time 0.

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Brain and Plasma Levels of MP. Intraperitoneal administration of [^{3}H]MP resulted in higher levels of radioactivity in plasma and brain than the intragastric route (Table 1).

View this table: [in this window] [in a new window]	TABLE 1 **d-[^{3}H]*threo*-MP or metabolite(s) concentrations (nmol/g) in brain and plasma after administration of 5 mg/kg MP via gavage or intraperitoneal injection**
	Values are mean ± S.D. Superscript letters correspond to post hoc *t* tests showing significant difference of intraperitoneal injection from gavage (oral).

Discussion

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This study shows that intragastric and i.p. routes of administration differ significantly with respect to the absolute magnitude and the time course of increases in extracellular DA and locomotor response. Intraperitoneal MP was approximately twice as potent as oral MP both in increasing extracellular DA levels at the doses of 5 and 10 mg/kg (Fig. 1A) and in stimulating locomotor activity at these same doses (Fig. 1B). This is

consistent with the apparent higher uptake of [^{3}H]MP measured in the brain after i.p. versus intragastric administration (Table 1). However, the interpretation of the brain uptake results is limited by the inaccuracy of assessing the total radioactivity counts without isolating [^{3}H]MP from ^{3}H-metabolites. Interestingly, at the lowest dose of 2 mg/kg given intragastrically, we did not observe an increase in DA levels above vehicle treatment nor was there any change in locomotor activity. In contrast, that same dose administered i.p. produced a significant increase above baseline values in extracellular DA and in locomotion. These data are in agreement with the notion that quantitatively different responses to identical doses of MP administered to humans via two systemic routes (i.v. and oral) are a function of bioavailability (Chan et al., 1980). The lower bioavailability for intragastric versus i.p. MP is presumably due to the slower absorption from the gastrointestinal tract and a greater degree of metabolism to ritalinic acid, a compound with negligible psychostimulant properties (Faraj et al., 1974).

Overall, quantitative and qualitative differences between oral, i.p., and i.v. routes of administration have been demonstrated for MP across species (Faraj et al., 1974; Wargin et al., 1983). However, the reports are varied and sometimes inconsistent. This may reflect considerable intersubject variability due to differences in drug absorption and metabolism. Studies by Faraj et al. (1974), Wargin et al. (1983), and Chan et al. (1980) provide evidence for presystemic metabolism of MP via deesterification in the gut and microsomal hydroxylation in liver as well as high intrinsic clearance due to plasma and/or tissue esterase activity. Reported estimates of the absolute systemic bioavailability of oral MP in children, rats, and monkeys vary between 10 and 50%.

Gross locomotor activity observed at 10 mg/kg i.p. does not seem to increase further with a higher dose of 20 mg/kg (O. Rice and S. J. Gatley, unpublished observations) even though extracellular NACC DA levels are increased further (860 versus 480% of baseline) (Rice et al., 1998). This is presumably due to focused stereotypies interfering with horizontal movements of the animal (Gaytan et al., 1996).

For both routes of administration gross locomotor activity responses to MP approximately track increases in NACC DA. This is consistent with the hypothesis that facilitation of DAergic transmission is involved in the locomotor response to psychostimulants (Beninger, 1983). The intragastric route exhibited a very close parallelism for the behavioral and neurochemical responses to MP, even though these measurements were obtained in different groups of animals. Normalized plots of extracellular DA and locomotor activity are almost identical (Fig. 6, A and B). However, for i.p. administration the quantitative features of MP-induced behavioral activation were dissociated from increases in extracellular DA. Peak hyperactivity occurred at 20 min postadministration, whereas the DA response took 40 min to reach its maximum. Between 20 and 40 min locomotor activity was

almost constant, whereas extracellular DA continued to increase. Although this could reflect a ceiling effect for locomotor activity, after which further DA increases result in stereotypies, it also could reflect acute tolerance to the locomotor-activating effects of synaptic DA, occurring after the fast initial increase in DA concentrations. A similar dissociation between plasma levels and therapeutic efficacy has been reported for oral MP in children (Swanson et al., 1999). The time course of plasma and brain MP concentration changes appears to be crucial in determining the efficacy of this drug (Srinivas et al., 1992). This notion was recently emphasized by Swanson et al. (1999) who demonstrated that the efficacy of a given total dose of MP is affected by its rate of administration.

A dissociation between DA and locomotor activity for the i.p. route of administration also was observed for the declining portion of the curves for the 10-mg/kg dose because at 120 min postinjection DA levels were already returning to baseline, whereas locomotion remained significantly elevated. This also could have reflected a ceiling effect and we cannot rule out the possibility that as DA levels fell stereotypy decreased concomitantly. New studies are now being designed with the goal of assessing the temporal course of stereotypies. Alternatively, this dissociation could reflect lingering downstream effects.

Another explanation is based on the partial involvement of the noradrenergic neurotransmitter system in the locomotor response to stimulants (Svensson and Ahlenius, 1983). We previously demonstrated that MP binds to norepinephrine transporters and is an effective in vitro inhibitor of norepinephrine uptake (Gatley et al., 1996). Kuczenski and Segal (1997) demonstrated that the temporal profile of the hippocampal norepinephrine response to i.p. MP in rats is significantly different from that of DA, with a slower onset and longer duration.

For the highest MP dose tested (10 mg/kg) the difference in locomotor activity between the two routes is better demonstrated by comparing the areas under the curve (total movements count over the sampling period) rather than the peak effects (Figs. 3 and 5) because the magnitudes of peak activity were similar, but i.p. MP had a much longer-lasting effect. This is likely to reflect almost complete DA transporter saturation at this dose for both routes, but the higher bioavailability achieved with the i.p. route may result in a longer duration of DA transporter blockade at this high level of occupancy.

In extrapolating the results of this study to the effects of clinical doses of MP the question of a proper dose for comparison arises. Matching of the peak MP plasma concentrations in humans and in rats does not seem to be appropriate for choosing a clinically relevant dose to be administered to animals. Concentrations that are considered therapeutic (8-10 ng/ml) (Swanson and Volkow, 2000) are reached at an average of 1 to 1.5 h after administration and roughly coincide with the peak changes in behavioral and somatic variables. The average half-life of oral MP is reported to be 2 to 3 h (Wargin

et al., 1983; Volkow et al., 1998). However, similar plasma levels in the rat are only achieved for a short period of time (1.4-25 ng/ml at 15 min) and are almost undetectable at 30 min (0-4 mg/ml) (T. Cooper, personal communication). According to Patrick et al. (1984), oral administration of 1 mg/kg MP in rats results in peak serum concentrations of 40 ng/ml that are reached 10 min after dosing, but which fall to 15 ng/ml during the next 5 min. However, when 10 mg/kg oral MP is administered to rats, the half-life of MP appears to be 1 h with the plasma levels of 40 ng/ml occurring 3 h after drug administration (Wargin et al., 1983) or 10 to 20 ng/ml 4 h after 20 mg/kg (T. Cooper, personal communication). Based on these data one might argue that the lowest dose of oral MP (2 mg) used in the present study is not of clinical relevance due to its short-lived effective concentrations in plasma and subsequently, brain concentrations. However, the intragastric dose of 10 mg/kg leads to sustained plasma levels that are higher than those achieved therapeutically. The intermediate MP dose of 5 mg/kg administered intragastrically might mimic the therapeutic doses better. In terms of the magnitude of neurochemical and behavioral effects, the 5-mg/kg intragastric dose was roughly equivalent to the 2-mg/kg i.p. dose. Thus, by extrapolation one could suggest that i.p. MP doses of less than 5 mg/kg may be closer to those used clinically. However, one should keep in mind that therapeutic effect of MP in humans requires sustained brain levels, which are not achieved in rats.

In this study we did not observe a difference between the DAergic responses to MP administered intragastrically or via gavage. This indicates that both methods are adequate for testing the effects of oral MP.

Investigation of the relative effects of oral and i.p. MP is of basic and clinical significance. Low reinforcing effects of oral versus i.v. MP in humans have been linked to differences in pharmacokinetics rather than poor binding efficacy at the DA transporter (Volkow et al., 1998). Additionally, several studies have shown that the effects of MP are dependent on the behavioral state of the subject. This effect described as "rate dependence" has been documented both in rats and in humans (Rapport et al., 1984; Weber, 1985). Our results demonstrate that the route of administration is an important determinant of the behavioral and neurochemical consequences associated with MP administration in rodents. Additionally, we are currently conducting new studies investigating the changes in brain DA elicited by therapeutic doses of MP in humans.

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Footnotes

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Abbreviations

MP, methylphenidate; DA, dopamine; LCGU, local cerebral glucose utilization; NACC, nucleus accumbens.

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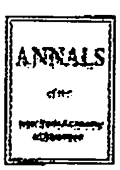

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C. J. HEYSER, M. PELLETIER, and J. S. FERRIS
The Effects of Methylphenidate on Novel Object Exploration in Weanling and Periadolescent Rats
Ann. N.Y. Acad. Sci., June 1, 2004; 1021(1): 465 - 469.

Americans Slightly Taller, Much Heavier Than 40 Years Ago

Adult Americans are roughly an inch taller than they were in 1960, but they are nearly 25 pounds heavier on average, according to a report issued by the Centers for Disease Control and Prevention (CDC).

The report, *Mean Body Weight, Height, and Body Mass Index (BMI) 1960-2002: United States*, shows that the average height of men ages 20-74 increased from just over 5 feet 8 inches in 1960 to 5 feet 9 1/2 inches in 2002, while the average height of women the same ages increased from slightly over 5 feet 3 inches in 1960 to 5 feet 4 inches in 2002.

Meanwhile, the average weight for men ages 20-74 rose dramatically, from about 166 pounds in 1960 to 191 pounds in 2002. The average weight for women the same ages increased from about 140 pounds in 1960 to 164 pounds in 2002.

The report, issued in October 2004, indicates that the average weight for men in 2002 compared to 1960 increased more among older men:

- Men ages 40-49 were nearly 27 pounds heavier.
- Men ages 50-59 were nearly 28 pounds heavier.
- Men ages 60-74 were almost 33 pounds heavier.

For women, the near opposite trend occurred when comparing average weight in 2002 with that in 1960:

- Women ages 20-29 were nearly 29 pounds heavier.
- Women ages 40-49 were about 25.5 pounds heavier.
- Women ages 60-74 were about 17.5 pounds heavier.

The report also documented a slight increase–less than an inch–in average heights for children over the last four decades. However, average weights for children increased significantly:

- Ten-year-old boys in 1963 weighed 74.2 pounds on average; by 2002 the group's average weight was nearly 85 pounds.
- Similarly, the average weight for 10-year-old girls in 1963 was 77.4 pounds; by 2002 their average weight was nearly 88 pounds.
- The average weight for 15-year-old boys in 1966 was 135.5 pounds; by 2002 their average weight was 150.3 pounds.
- Fifteen-year-old girls on average weighed 124.2 pounds in 1966; by 2002 their average weight was 134.4 pounds.

Average body mass index (BMI) has also increased among adults from about 25 in 1960 to 28 in 2002. BMI is a number that represents an individual's weight in relation to height. BMI is generally used as the first indicator in assessing body fat and has been the most common method of tracking weight problems and obesity among adults. A BMI of 18.5 to 25 refers to a healthy weight, those with a BMI of 25 to 30 are considered overweight, and people with a BMI of 30 or higher are classified as obese.

The average BMI for children and teens has increased as well:

- In 1963, the average BMI for 7-year-old boys was 15.9; in 2002 it was 17.0. For girls the same age, the average BMI increased from 15.8 to 16.6 over the same period.
- In 1966, the average BMI for 16-year-old boys was 21.3; in 2002, it was 24.1. For girls the same age, the average BMI increased from 21.9 to 24.0 over the same period.

The data in the report were based on actual body measurements taken as part of the National Health and Nutrition Examination Survey, which the CDC's National Center for Health Statistics has conducted periodically since 1960.

For More Information

Mean Body Weight, Height, and Body Mass Index (BMI) 1960-2002: United States (620 KB PDF file)

www.cdc.gov/nchs/